

BOOK REVIEW

PAUL EHRLICH. By Martha Marquardt

With an Introduction by Sir Henry Dale, O.M., G.B.E., M.D., F.R.S.

[1949. William Heinemann, London. Pp. 254, 50 illustrations. 25s.]

This is a delightful book, written by the lady who was Ehrlich's private secretary for the last thirteen years of his life. She describes it as an enlargement of her earlier work, "Paul Ehrlich als Mensch und Arbeiter", published on March 14, 1924, the 70th anniversary of his birth and about eight and a half years after his death.

It does not pretend to be a full biography—such a work in Ehrlich's case would occupy more than one large volume—but it gives enough detail to enable the reader to form an intimate mental picture of a great genius, one of the few people who have mattered to the world in the past century. One may reasonably wonder how comparatively poor would be our remedial resources today if Ehrlich had not opened the gate into the great field of chemotherapy.

The author acknowledges indebtedness to the late Sir Almroth Wright for having made it possible for her to come to London to finish the present work, and to Sir Henry Dale for encouragement and help. She also thanks Miss Johnston Abraham for revising her English, a collaboration which, if I may say so, has been most successful, for the book is eminently readable. Its value is enhanced by the illustrations, of which fifteen depict Ehrlich in different periods of his life, most of the remainder being portraits of scientists and patrons associated with Ehrlich in his work.

Sir Henry Dale's introduction is a valuable feature. It puts Ehrlich's work and ideas in their right perspective in the scientific field. Besides mentioning his great service in the improvement and standardization of antitoxins, he shows how Ehrlich's early work with dyes laid the foundation of all chemotherapy, a science that has now reached the stage of antibiotics. Sir Henry also draws attention to what might be regarded as a useful complement to the book under review, an exposition of his scientific work, entitled "Paul Ehrlich. Eine Darstellung seines wissenschaftlichen Wirkens", a

symposium in honour of Ehrlich's 60th birthday, written by 37 men who had been associated with him in different aspects of his work. I could wish that someone would translate this birthday symposium into English and condense the different articles to make a book that could be read fairly quickly these rapid times; it would be a most valuable stimulant to research workers and a corrective to the get-known-quickly people. Sir Henry expresses a hope that one day we may have "a complete assembly, in one edition, of all his not very voluminous publications". One could well wish that this might be brought about, though Miss Marquardt mentions that from 1877 to 1914, Ehrlich published 232 papers and books (listed in the birthday symposium) and the compilation would be rather formidable. Sir Henry confesses that on reading Miss Marquardt's manuscript, he "did wonder indeed, whether some of the detailed accounts of Ehrlich's resentments and grievances, or of his anger, on occasion, with colleagues who were not just tamely obedient, ought not to be removed, or subdued, in the interest of a true impression of his greatness". He concludes, however, by expressing agreement with her retention of these passages. I would certainly agree with her inclusion of the passages in question as their omission would have left the picture too smooth; I would say this although I believe, without abating any of my reverence for Ehrlich's genius, that the prime causes of two clashes with colleagues related by Miss Marquardt were orders given by Ehrlich which were troublesome and unnecessary; on this I will dilate later.

Miss Marquardt opens with Ehrlich's birth—(March 14, 1854)—in Strehlen, Silesia and traces his likeness, in his lively mannerisms and gesticulations in his youth and throughout his life, to his father, an innkeeper; and in his geniality, hatred of injustice, sound judgment and other good qualities to both of his parents and a grandfather. From

the latter he appears to have inherited his taste for natural science—incidentally, Karl Weigert, the great pathologist was his cousin. Knowing what we do of the immense loyalty he commanded throughout his life and the enthusiasm with which he inspired disciples from many lands, it is not surprising to read that, as a boy, he was the acknowledged leader of the boys from seven to sixteen years of age in his neighbourhood, fertility of ideas for new activities being appreciated at all ages. Many who read this book may take heart from the fact that, although he shone brightly in Latin, mathematics, and chemistry, he was (like Pasteur before him) a rather indifferent examinee. He recognized the limitations of the brain and concentrated on the subjects for which he had ability, considering that time spent on others in which he had no real interest was largely wasted. As a student he learnt chemistry very easily, and very soon became absorbed in experiments with aniline dyes—at that time he was once pointed out to a visitor, the great Robert Koch (whom he later assisted for some years) thus: That is “little Ehrlich”. He is very good at staining but he will *never* pass his examinations. It is interesting to speculate whether his interest arose primarily from his well-known love of bright colours or his innate scientific curiosity over the effect of varying chemical formulae, or both. He appears to have pictured the chemical compounds in which he was interested as edifices with their constituent molecules arranged as in a graphic formula and to have found their permutations a fascinating study, particularly perhaps when the results were coloured. He qualified in 1878, and the title of his thesis showed his bent: “Contributions to the Theory and Practice of Histological Staining. Part I. The Chemical Conception of Staining. Part II. The Aniline Dyes from Chemical, Technological and Histological aspects.” Of three commentaries on this thesis which Miss Marquardt quotes, perhaps the most appropriate for the purpose of this review is that by his friend, Prof. L. Michaelis, Berlin, who found the thesis after Ehrlich's death, by searching through the Archives of the University of Leipzig.

Paul Ehrlich has here defined his decided attitude towards the purely chemical conception of the staining process; and in his reflections about the nature of the staining, the ‘*idea of a chemical binding of heterogeneous substances to the protoplasm*’ was born. This idea was quite logically developed into his Side-Chain Theory; . . . He worked all his life to prove this idea was right, and in doing so he discovered many facts which can never perish or disappear but will outlast all Time.

Miss Marquardt says rightly at the end of this chapter:

What Ehrlich stated in this graduation thesis recurred again and again in his later writings in one form or another, and ran like a ‘red strand’ through all his publications.

Many years later when he had become famous throughout the world, visitors to his laboratory often remarked on the simplicity of his apparatus, just some test-tubes, a Bunsen burner, multitudes of chemicals in a forest of bottles, and the blotting paper on which he would drop the coloured results of his experiments. He was never trained as a professional chemist, and L. Benda, a chemist lent to him in later years by the Cassella Chemical works (later incorporated in the I.G. Farbenindustrie) is quoted by Miss Marquardt as having said in the birthday symposium already mentioned that he was a “virtuoso in the art of test-tube experiments”. Benda also wrote:—

Ehrlich is self-taught as a chemical investigator but he is ‘the born chemist’. The happy union of the prominent biological and medical investigator and the distinguished chemical worker, as we see it in Ehrlich and are unlikely to find it a second time, has turned out to the benefit of both disciplines, medical and chemical.

Miss Marquardt quotes also from an earlier paragraph of Benda's article:

To work with Ehrlich is a real pleasure. The tenacity with which he holds on to an idea, seizes a problem and sticks to it until he has solved it, has a powerful effect on his fellow-workers. His optimism which saves him from being down-hearted in cases of failure (with which every investigator must reckon) is transmitted to his pupils. How often, when a chemical preparation in which he had great confidence and hope proved too toxic, or insufficiently effective, did he encourage us, saying: ‘If we now introduce chlorine, or if we eliminate the sulphonating groups, we shall have what we want’. And we added chlorine, eliminated sulphonating groups, and—often attained what we wanted.

The evolution of a chemical reaction to be used as a test seems to have been rather a matter of trial and error. Thus, Miss Marquardt describes casually the evolution of the Ehrlich dimethylamidobenzaldehyde test which became so well known to syphilologists in the bad old jaundice days. In the midst of dictating an article, he disappeared into his, adjoining, laboratory and as he did not quickly return Miss Marquardt followed him. He was heating some solution in a test-tube and presently handed her the tube to hold. He repeated these manoeuvres a number of times, varying the technique a little each time until her hands were quite full of test-tubes containing solutions of, doubtless,

varying colours. Eventually he was satisfied (he was not easily satisfied and precision of technique was a strong feature of all his work) and then began to dictate the technique of the test, in a letter to E. Merck, Darmstadt. Miss Marquardt in that situation might have been likened to Beau Brummell's servant, who, discovered by a morning caller leaving Beau Brummell's room with an armful of crumpled neckcloths, explained: "These are our failures, Sir."

To concentrate a little on Miss Marquardt's fascinating description of Ehrlich's personality, we learn that whilst he was working at the Charité-Hospital, Berlin, he married [1883] a Silesian lady, Hedwig Pinkus, whom the author describes as "a lovely, faithful and understanding companion for the rest of his life". If she was at all house-proud, she must have been very loving or very understanding or both to put up with an absent-minded chain-smoker of strong Havana cigars (at least 25 a day). The author's account of a typical day in Frankfurt in 1903 started in Ehrlich's study at his home, in a thick fog of cigar smoke following him from his adjoining bedroom; every chair (but one) and both tables of the study littered with papers and books, and Ehrlich smoking continuously, allowing his breakfast (placed on a partially cleared small table) to become quite cold whilst he gave his factotum, the discreet Kadereit, the day's orders and suggestions for his assistants, each assistant's instructions written out on a card. He always went to and returned from his institute in a horse-drawn cab, the driver of which seems often to have been bribed by Frau Ehrlich to take her absent-minded husband a little further round on the return journey to give him some fresh air. In the evening he would be chaffed by his two daughters for some absent-minded action or for his extravagant private abuse of some scientific opponent. His favourite diversion until 10 p.m. appears to have been simple music (he liked barrel-organ music and would hum tunes, generally out of tune) or a patience game which was played on his own original lines and never came out, or (once weekly) the instalment of a murder thriller—he was a Sherlock Holmes fan. At 10 p.m. he settled down again to work till midnight or later. As one reads this fascinating book, one acquires quite an affection for his caretakers, if one may call them so; for the faithful Kadereit, brought with him from Berlin to Frankfurt, and for Dora, who brings in the breakfast, clearing a small place for the tray on a little table; calls the cab to take the Herr Geheimrat to the institute and when he has to go to a party in the evening unaccompanied by any of his family, gives the caddy his instructions, with the fare, to insure

that the professor is delivered safely to his hosts. Dora again, who is there some years later to carry off the grandchildren to bed. Miss Marquardt reveals at many points evidence of Ehrlich's kindly nature, his subsidizing of lame dogs, his help to aspirants in professions other than his own, his love of children and the trouble he took to amuse them, as also his hatred of injustice and his terrier-like reaction to stupidity in opposition. Miss Marquardt has put her readers under a large debt of gratitude for her picture of a very lovable man, a giant in science, a child in his lack of self-consciousness, in his freedom from pomposity and in his enthusiasm, though withal occasionally rather childish when crossed in his work plan.

Nearly ten pages are devoted to Ehrlich's work in making von Behring's discovery of antitoxins in the serum of animals immunized against diphtheria and against tetanus of practical service by the invention of methods to increase and measure the potency of the antitoxins; also to grievance over Behring's attempts to exploit Ehrlich. Some cutting things are said in this section, and the photograph of von Behring on p. 31, with all his goods in the shop window—retort, flasks, microscope, four guinea-pigs, and manuscript all posed for the photographer—says more than could many lines of print.

The description of Ehrlich's work which led to the synthesis of 606 does not seem to do justice to the fact that it was the reports of Thomas and of Thomas and Breinl, Liverpool, on the effect of atoxyl on trypanosomiasis in animals which started him off on the path which led to 606. These results were published in 1905 (not 1906 as stated by Miss Marquardt) and although it is stated in this book that before the Speyer-Haus was built (it was opened in 1906) Ehrlich had already found that the chemical constitution of atoxyl was not as described by Béchamp in 1863, one judges from Berthelm's articles in the birthday symposium and his definite statement on p. 448 that it was after publication of the Liverpool results that Ehrlich again turned his attention to atoxyl and found that it reacted with his diazo reagent, a result incompatible with the Béchamp formula. His instruction to the chemical staff of the newly-opened Speyer-Haus to work out the formula caused one of the breezes described by Miss Marquardt. Two of the three chemists walked out, stupidly saying, without trying, that they believed the Béchamp formula to be correct, but the third, Berthelm, remained and the correct formula was published by Ehrlich and Berthelm in 1907. Miss Marquardt does not speculate on the reason for the attitude of the Speyer-Haus chemists but one might guess reasonably that at that time they regarded Ehrlich as a mere amateur and

would not take orders from him regarding details of their branch of work. The incident says much for Ehrlich's backbone; it must have been a pleasure to work with a chief who was no mere shadow!

I find it difficult to follow Miss Marquardt in the opening paragraph of Ch. XIV where she says, speaking apparently of a period before 1906, that atoxyl had been found to have a highly toxic effect on the optic nerve. It is difficult to believe that this toxic effect had been noted so early as that because atoxyl was used extensively for the treatment of syphilis until the end of 1909 when the toxic effects just noted began to be reported; as I have noted elsewhere, we saw no such effect at the Military Hospital, Rochester Row. I regret having to join issue with Miss Marquardt but in the interest of historical accuracy must submit that, but for the work of Thomas and Breinl, the formula of atoxyl would not have been re-examined in 1906, and the long train of experiments which led to 606 would not have been started then.

This detracts in no way from Ehrlich's reputation. It was his genius which detected the significance of the Liverpool results and of the reactivity of atoxyl to his diazo test, the possible end of a thread which might lead to his goal, the *therapia sterilisans magna*, the remedy with a selective action on spirochaetes and a relatively slight affinity for human tissues. It may be interesting to remark here that a little more than thirty years previously, another genius, Louis Pasteur, had seen in the loss of virulence of hen cholera cultures as a result of ageing and in the fact that hens which had survived inoculation with this attenuated culture resisted inoculation with virulent strains, a controllable means of protecting by inoculation against infection. One of Ehrlich's favourite sayings was that the essentials for success in research work were: *Geduld, Geschick, Geld, und Glück*. (Patience, ability, money and luck.)

Miss Marquardt records that before Hata tested 606, a predecessor had reported on it unfavourably and that for more than a year it had been laid aside as ineffective.

The story of Ehrlich's reactions to reports of untoward effects of 606 must be enormously interesting to anyone who, like myself, was at the periphery actively engaged in finding how to use 606 to the best advantage. The idea that a comparatively few side-effects could give 606 a bad name and cause such a scene as that described on pp. 198 and 199 seems to me unbelievable and one cannot help thinking it a pity that Ehrlich wore himself out fretting over happenings which a sense of proportion would have told him were comparatively unimportant. In the light of after-wit, a

small committee of level-headed clinicians and chemists should have dealt with the "complaints". It was faulty judgment that laid the blame for necrosis of tissue at the sites of intramuscular injections of 606 on bad technique or the use of stale water in making up the injected mixture. The fact is that 606 is inherently necrosing and the marvel is that more sloughs than we saw did not occur.

It seems rather a pity that Miss Marquardt has not given the credit for saving the 606 situation to Iversen (St. Petersburg) and Schreiber and Hoppe (Magdeburg) who independently adopted the intravenous route; but for this the use of 606 would have been greatly restricted because of the pain it caused locally and the danger of sloughing. In the original articles by these workers I found no evidence of this route having been suggested by the Frankfurt Institute. I find it difficult to follow Miss Marquardt in her account of the enquiries about the kind of water used for intramuscular injection. My strong recollection (supported by Nathan in Kolle and Zieler's "*Handbuch der Salvarsan Therapie*", vol. 1, p. 525) is that this question of stale water first arose in connexion with the reactions following intravenous injections of 606, and that it was Wechsellmann who first advanced the explanation that they were due to the bodies of germs which had multiplied in the distilled water stored in laboratories or in pharmacies, with which the 606 was made up for injection. Certainly this water was sterilized but Wechsellmann had been impressed by the work of Vaughan *et al.* (Missouri) on the toxic effects of proteins (including those of bacteria) when injected parenterally. So far as my own searches are concerned, Vaughan's first publication on this subject was in 1896 but it happened that he and colleagues published a paper on similar lines in *Zeitschrift für Immunitätsforschung*, (1911, Orig. 11, p. 673.) and it was to this paper that Wechsellmann referred in his article in *Münchener medizinische Wochenschrift* (1911, 58, 1510).

I have mentioned some difficulties which Ehrlich had with his chemical colleagues over orders which I suggested may have been unnecessary. They concerned the elimination of oxygen. The first of these was in the making of arsenophenylglycin and the order was first given orally to Bertheim during a visit by Hoffmann, being confirmed in writing the next day on one of Ehrlich's cards. The author records that Bertheim tore this order up and disregarded it until Ehrlich took up the matter with him somewhat heatedly. How that was settled is not stated but the difficulty recurred in connexion with the making of 606. The author here says:

In order to avoid oxidation during the various processes of manufacture of 606 in the Speyer-Haus, Ehrlich insisted that as well as carrying out the various manipulations in a perfect vacuum

and he wrote to Dr. Kahn the head of the Chemical Section to this effect, following it up orally thus :

It is absolutely necessary and extremely important to take even more precautions than before in the preparation of 606. In the intervals between the different operations the products must not be kept merely in the refrigerator but actually packed directly into the ice. Only in this way can we be certain of avoiding oxidation throughout the different phases of the manufacture.

Kahn neglected this instruction and apparently for this reason left the Speyer-Haus. It seems strange that these trained chemists, dealing with a product which was to be given to human beings, should have neglected to carry out such precise instructions if they did not think Ehrlich's precautions too elaborate and actually unnecessary.

To a non-chemist, like myself, it is not easy to understand why there was any need for precautions against oxidation before the product had been reduced to the salvarsan base by treatment with sodium hydrosulphite. In this form it is insoluble in water and presumably inactive. From it is made the dihydrochloride by solution in methyl alcohol and hydrochloric acid, and 606 is precipitated out of this solution by admixture with ether. Until this has been driven off there still seems to be no opportunity for oxidation or need to take special precautions against it.

This impression seems to be supported by Berthelm in the birthday symposium already referred to in which he said (p. 469)

. . . the solution of the base in hydrochloric acid, filtration of the solution, the precipitation and isolation of the hydrochloride under air-exclusion in a stream of indifferent gas, the preparation is cautiously dried and forthwith sealed in a vacuum tube ; also there were very large quantities of liquid, particularly of ether with its dangers of fire, to be managed. . . .

Even the use of an indifferent gas and sealing *in vacuo* seems in the case of 606 (very unlike 914) to have been unnecessary. Certainly the 606 of German make which I found in bulk at Creil during the war of 1914-18 was in large glass bottles with bungs, and the French brand of 606 (Arsenobenzol (Billon)) of which very many thousands of doses were used in the British army during that war was not sealed *in vacuo* ; when I enquired the reason, the makers (Messrs. Poulenc Frères) explained that they had found the ether vapour remaining after the drying of the powder sufficient to prevent oxidation. The fact is that 606 does not become

toxic very quickly when exposed to air. Even when alkalinized, a state in which it is acknowledged to be most vulnerable from this point of view, it does not become dangerous for some hours. At any rate, prior to 1914, when only German 606 was being used in this country, a firm of retail chemists in London told me that regularly they made it up ready for injection and despatched it by passenger train to an address four hours away ; I should not have dared to use such an old solution.

These remarks are by way of suggesting that perhaps the resistance of the chemists in the Speyer-Haus to the orders mentioned above arose from a feeling that they were unnecessarily meticulous and perhaps impracticable. Berthelm's article just quoted reveals the difficulties under which 606 was made in the trial period before the whole manufacture was taken over by the Höchst Farbwerke. He said (p. 468) : " A scientific laboratory is little adapted for a factory operation even when this is on very moderate lines." It seems probable that the chemists were hard-pressed and their tempers a little frayed.

Altogether, one cannot escape the impression that Ehrlich attempted too much in trying to supervise and guide the manufacture, despatch and administration of 606 in detail, and that thereby he not only ruined his health but in some respects impaired his judgment. If he had left those details to smaller men, as I believe would have been quite safe, he might have been spared to give the world an improvement on silver-salvarsan.

But perhaps not ; twenty-five Havana cigars a day, washed into his system with mineral water ; no exercise to speak of ; few holidays ; and indifference over food must tell in the long run ; and the portrait, on p. 244, of Ehrlich at the age of 60 is such as might have been expected.

One great feature I have not emphasized sufficiently which is well brought out by Miss Marquardt ; it was Ehrlich's simplicity and lack of any kind of pomposity or professorial demeanour. When one thinks of the unassuming great men with whom we have been blessed in the past century, one could wish that the strutters, the jacks-in-office, and the like could be made to study such biographies as this, that they might learn how the really great comport themselves.

The book would be improved by provision of a good index, but I hope this review will win many readers for it and I should like to acknowledge indebtedness to Dr. Forgan and to the staff of Messrs. May and Baker for very kindly verifying my reference to Arsenobenzol (Billon) and my remarks on precautions against oxidation of 606.

L. W. H.